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PERINEAL TALC EXPOSURE AND EPITHELIAL OVARIAN CANCER RISK IN THE CENTRAL VALLEY OF CALIFORNIA

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Perineal talc use has been suggested as a possible risk factor for ovarian cancer based on its structural similarity to asbestos, a known human carcinogen. A population-based epidemiologic case-control study of epithelial ovarian cancer (EOC) was conducted in 22 counties of Central California that comprise the reporting area for 2 regional cancer registries. Telephone interviews were conducted with 256 cases diagnosed in the years 2000–2001 and 1,122 controls frequency-matched on age and ethnicity. The interview obtained information on demographic factors, menstrual and reproductive experience, exogenous hormone use, surgical history and family history of cancer. Questions on perineal talc use included frequency of use, duration of use and specific years when talc was used. Multivariate-adjusted odds ratio (OR) and 95% confidence intervals (CI) were derived from unconditional logistic regression. The OR for ever use of talc was 1.37 (CI = 1.02–1.85) compared to never users. However, no dose response association was found. Tubal ligation (TL) modified the effect of talc on EOC such that women with TL had an OR of 0.88 (CI = 0.46–1.68) associated with perineal talc use, whereas women with no TL had an OR of 1.54 (CI = 1.10–2.16). Talc use and EOC risk was highest in women with serous invasive tumors (OR = 1.77; CI = 1.12–2.81). This study provides some support for the hypothesis that perineal talc use is associated with an increased risk of EOC.
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Interest in the relationship between talcum powder and ovarian cancer risk is based on certain physical properties of talcum powder, including the fact that talc is mineralogically similar to asbestos and that talcum powder manufactured before 1973 may have been contaminated with asbestos.[1] In animal studies, talc and other similar substances have been demonstrated to migrate from the vagina through the peritoneal cavity to the ovaries.[2] Henderson *et al.*[3] also observed that particles with the appearance of talc were more prevalent in ovarian tumors than in normal ovarian tissue. Several epidemiologic studies have investigated perineal use of talcum powder as a potential risk factor for ovarian cancer and most have found elevations in risk, although there has been a large range in the risk estimates, from 1.1 to 3.9.[4] Collectively, these studies point to a possible etiologic role of talc in ovarian cancer via an inflammatory process at the site of the ovarian epithelium,[5] although recall bias may play a role in retrospective studies.[4] Inflammation produces oxidants that are thought to damage DNA and Ames *et al.*[6] argue that damage to tumor suppressor genes caused by the inflammatory process leads to carcinogenesis. Chronic inflammation may also result in deregulated cytokine production, which may result in altered cell growth, inhibition of apoptosis and changes in differentiation.[7]

Cramer *et al.*[8] proposed 2 mechanisms that might explain talc carcinogenesis. Talc may stimulate the entrapment of the ovarian surface epithelium, thus mimicking what occurs during ovulation and posing a risk similar to that proposed by incessant ovulation.[9] Alternatively, if talc is present at the time of ovulation, it may become incorporated into the inclusion cyst. It has been suggested that foreign-body exposure may result in granulomas[10] and that pure talc may induce granulomas in open wounds.[11] Granulomas are also associated with persistent acute inflammatory responses.[12]

The role of cornstarch powder on ovarian cancer risk has also been evaluated in epidemiologic research and a recent review concluded that there is no association between this type of powder and increased risk of ovarian cancer.[13] The conclusion was based on a total of 4 case-control studies that elicited information on use of cornstarch in perineal dusting, in which the average odds ratio was 0.62. However, there were only a total of 20 cases of ovarian cancer combined in those studies and 51 control subjects. Cornstarch is also not thought to exert the same toxicologic reaction in human tissue as does talc.[13]

MATERIAL AND METHODS

A population-based epidemiologic case-control study of epithelial ovarian cancer (EOC) was conducted in 22 counties of Central California that comprise the reporting area for 2 regional cancer registries. Geographically, these counties make up the majority of the Central Valley of California, which is the poorest area of the state, with many residents living below the poverty level.[14] Demographically, the Valley is a very ethnically diverse area in which many counties are over 40% Hispanic. Two population-based cancer registries have monitored cancer incidence in the Central Valley of California continuously since 1988: the Cancer Registry of Central California (CRCC) in Fresno and the Cancer Surveillance Program (CSP), Region 3, in Sacramento.[15,16] All newly diagnosed histologically confirmed EOC patients were available for inclusion in this study for the years 2000 and 2001.

Cases were women-identified via a rapid case ascertainment (RCA) procedure as having been diagnosed with EOC (malignant neoplasms of the ovary, ICD-O 3 = C56.9) living in the Central Valley during a 24-month period from 1 January 2000 through 31 December 2001. Tumors were designated as borderline if the behavior code was designated as 1, or if the pathology report described the tumor as borderline, low malignant potential, or atypically proliferating.[17] The borderline classification was limited to serous and mucinous cell types because ICD-O 3 has no morphology code for the borderline classification in the other subtypes and because serous and mucinous tumors make up the majority of borderline tumors.[18] All other tumors were classified as invasive.

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Histologic subtypes were identified by pathologic report or by ICD-O 3 morphology codes. The histologic subtypes included were serous, mucinous, endometrioid, clear cell and other epithelial/unclassified. The latter category included unspecified adenocarcinomas as well as undifferentiated tumors in which a cell type could not be classified histologically. All newly diagnosed EOCs of epithelial origin were identified via RCA methods in which hospital tumor registrars were asked to provide listings of newly diagnosed EOCs within 1 month of diagnosis. A board-certified pathologist reviewed the pathology reports of a sample of cases. Physician consent was obtained by mailing the physician of record a letter and informing him/her that an interview with the patient was planned. If the physician did not respond within a 3-week period, passive consent was assumed. The control group consisted of women 18 years or older selected by random digit dialing (RDD) techniques who were residents of the area, had not been diagnosed with EOC and had at least one intact ovary at the time of the interview. Controls were frequency matched to cases on age and race/ethnicity. The overall data collection period covered a 2-year period, with each respondent being interviewed only once during this period by telephone. Interviews were conducted with both cases and controls on a monthly basis throughout the 2-year period.

All cases and controls were approached via an introductory letter that included a prompt list that described topics the interview questions would address. The Institutional Review Board at the Public Health Institute approved the study protocol. For both case and control groups, letters and prompt lists were sent in either English or Spanish on the letterhead of the principal investigator. Telephone interviews with both case and control respondents were conducted by female professional, trained telephone interviewers in either English or Spanish as preferred by the respondent.

The interview obtained information on demographic factors as well as information pertinent to the respondent's menstrual and reproductive experience, use of exogenous hormones, gynecologic surgical history and family history of cancer. Four questions were asked in regard to the use of talcum powder, including adult use in the genital area, calendar year(s) of use, frequency of use (*i.e.*, daily, several times a week) and total duration of use. The last 2 questions were used to create a variable reflecting—cumulative use by combining frequency (categorically weighted 0–3) and duration (in months) of use.

Age-adjusted odds ratios were calculated using the Mantel-Haenszel method.[19] Multivariate adjusted odds ratios were calculated using unconditional logistic regression.[20] Initially, multivariate models were constructed to include age as a continuous variable and race/ethnicity, duration of use of oral contraceptives, duration of breast-feeding, history of breast or EOC in a first-degree relative, pregnancy history, parity, body mass index (BMI), hysterectomy, tubal ligation and duration of hormone replacement therapy use as categorical variables. However, the Hosmer-Lemshow goodness-of-fit tests revealed that after terms for duration of oral contraceptive use and duration of breast-feeding were added to the models, fit was not improved by the addition of the other variables listed above. Nor were the estimated odds ratios altered by the addition of the several variables listed above. Therefore, in the interest of parsimony, the final models chosen for the analysis included terms for age, race/ethnicity, oral contraceptive use and breast-feeding. Interaction was assessed by comparing stratum-specific odds ratios. If the stratum-specific odds ratios differed by more than 100%, interaction was also assessed by including first-order cross product terms into the logistic model and examining the significance of the interaction coefficient. Tests for trend were conducted for variables that were ordinal in nature by recoding the categories into continuous form and evaluating the Wald statistic associated with the resulting coefficient. Confounding was assessed by examining the differences in the crude, age-adjusted and multivariate-adjusted odds ratios.

RESULTS

The regional cancer registries initially identified a total of 652 cases of confirmed epithelial ovarian cases residing in the 22 county study area diagnosed between 1 January 2000 and 31 December 2001. Seventeen cases were excluded due to speaking a language other than English or Spanish or due to hearing/speech impairment, resulting in 635 cases that met the study criteria. Seventy-six cases died prior to research contact and physicians refused permission to contact for 10 cases. Forty-one cases were too ill to participate in the study and 119 were not contacted due to incorrect telephone numbers or no answer after repeated efforts. Of the remaining 389 cases, 133 refused to participate, resulting in 256 completed interviews. Therefore, the response fraction was 40% among all cases identified. There were no significant differences in age ($p = 0.273$) or level of invasiveness between interviewed and noninterviewed cases. Histologically, interviewed cases were more likely to be of the serous subtype (57.4% for interviewed cases, 45.6% for noninterviewed cases) and less likely to be classified as "other epithelial" (10.5% for interviewed cases; 22% for noninterviewed cases). There was no statistically significant difference between interviewed and noninterviewed cases for the other histologic subtypes. Information on perineal talc use was missing in 7 cases.

Households with eligible women were identified through RDD methods, resulting in 2,327 controls identified and sent an introductory letter with a prompt list. Eighty of these women were later found not to meet the age requirement and 21 were ineligible due to residence outside the study area. Ten controls were excluded due to speaking a language other than English or Spanish. Two hundred fifty-two controls were excluded due to reporting bilateral oophorectomy, resulting in 1,964 controls that met the study criteria. Nineteen controls were too ill to participate and 358 were later found to have moved, changed phone numbers, or failed to answer after repeated efforts. Of the remaining 1,587 contacted controls, 465 refused to participate, resulting in 1,122 completed control interviews for a response fraction of 57% for total identified eligible controls. Information on perineal talc exposure was missing in 17 controls.

Invasive tumors constituted 71.1% of the case series and 28.9% of the tumors were of borderline malignancy. Among non-Hispanic white women, who constituted 74% of the cases, 25.8% were of borderline invasiveness. Overall, 57% of the case series were serous adenocarcinomas, divided 60% and 40% for invasive and borderline, respectively. Mucinous and endometrioid each comprised 14% of the EOC cases. There were slightly more mucinous borderline cases than invasive cases. Clear cell and other/unclassified histologies made up the remaining 5% and 11%, respectively.

The demographic characteristics of all cases and controls and cases and controls stratified by talc exposure are shown in Table I. Matching was successful and cases and controls were similar in age and ethnicity. Controls were less likely to have finished high school but more likely to have an education beyond high school. A somewhat larger proportion of the case series were single (12.5%) compared to the control series (10.0%). Control women were more likely to have been born outside of the United States (16.8%) than were cases (12.9%).

A total of 42.6% of EOC cases reported ever use of talcum powder in the perineal area while 37.1% of control women reported such a history. Case women using talc were slightly older at interview than controls. Women in the oldest age group used talc less than younger women, much more so for control women than case women. White non-Hispanic women were more likely to use talc than their Hispanic counterparts. Talc use was higher in both white non-Hispanic and Hispanic cases compared to controls but this pattern was not seen in the "other" ethnic category. Talc use was also associated with a higher education level. Talc use was higher in both cases and controls with birthplace in the United States.

TABLE I – DESCRIPTIVE CHARACTERISTICS OF EOC CASES AND CONTROLS IN CALIFORNIA'S CENTRAL VALLEY BY TALC EXPOSURE, 2000–2001

Characteristic	Cases		Controls	
	Total[1]	Talc exposure, *n* (%)	Total[1]	Talc exposure, *n* (%)
Number of subjects	249	106 (42.6)	1105	410 (37.1)
Mean age at interview	56.6	56.6	55.0	53.7
Age group (%)				
< 40	20	7 (35.0)	112	43 (38.4)
40–49	66	34 (51.5)	317	121 (38.2)
50–59	57	20 (35.1)	268	113 (42.2)
60–69	56	25 (44.6)	211	82 (38.9)
≥ 70	50	20 (40.0)	197	51 (25.9)
Ethnicity (%)				
White non-Hispanic	187	85 (45.5)	802	317 (39.5)
Hispanic	42	15 (35.7)	201	54 (26.9)
Other	20	6 (30.0)	102	39 (38.2)
Education (%)				
< high school graduate	33	13 (39.4)	208	60 (28.8)
High school graduate	84	34 (40.5)	261	99 (37.9)
> high school graduate	130	59 (45.4)	635	251 (39.5)
Marital status (%)				
Single	32	11 (34.4)	111	40 (36.0)
Married	133	59 (44.4)	670	246 (36.7)
Divorced/separated	40	17 (42.5)	175	77 (44.0)
Widowed	44	19 (43.2)	145	46 (31.7)
Birthplace (%)				
In United States	216	96 (44.4)	919	379 (41.2)
Outside United States	33	10 (30.3)	186	31 (16.7)

[1]Numbers may not add up to total cases and controls due to missing data.

TABLE II – FREQUENCIES, MULTIVARIATE-ADJUSTED ODDS RATIOS AND 95% CONFIDENCE INTERVALS FOR PATTERNS OF TALC USE FOR EOC CASES AND CONTROLS, CENTRAL VALLEY OF CALIFORNIA, 2000–2001

Patterns of talc use	Cases (%) (n = 256)[1]	Controls (%) (n = 1,122)[1]	Multivariate-adjusted OR (95% CI)
Talc use			
Never	143 (57.4)	695 (62.9)	1.0
Ever	106 (42.6)	410 (37.1)	1.37 (1.02–1.85)
Frequency of use			
Never	143 (57.4)	695 (63.2)	1.0
Rarely to several times per month	34 (13.7)	138 (12.5)	1.34 (0.87–2.08)
1–3 times per week	31 (12.4)	145 (13.2)	1.16 (0.74–1.81)
4–7 times per week	41 (16.5)	122 (11.1)	1.74 (1.14–2.64)
			Trend p = 0.015
Duration of use			
Never	143 (58.9)	695 (64.2)	1.0 (referent)
≤ 3 years	18 (7.4)	99 (9.2)	1.01 (0.58–1.76)
4–12 years	32 (13.2)	98 (9.1)	1.86 (1.16–2.98)
13–30 years	29 (11.9)	102 (9.4)	1.45 (0.90–2.32)
> 30 years	21 (8.6)	88 (8.1)	1.22 (0.72–2.08)
			Trend p = 0.045
Cumulative use (frequency × duration)			
Never	143 (58.9)	695 (64.4)	1.0 (referent)
First quartile (lowest exposure)	18 (7.4)	95 (8.8)	1.03 (0.59–1.80)
Second quartile	28 (11.5)	95 (8.8)	1.81 (1.10–2.97)
Third quartile	34 (14.0)	107 (9.9)	1.74 (1.11–2.73)
Fourth quartile (highest exposure)	20 (8.2)	88 (8.1)	1.06 (0.62–1.83)
			Trend p = 0.051

Adjusted for age, race/ethnicity, duration of oral contraceptive use and breast feeding. [1]Numbers may not add up to total cases and controls due to missing data.

Ever use of talcum powder in the genital area was associated with a 37% elevation in risk of EOC, which was statistically significant (Table II). Increasing frequency of use was associated with increasing risk such that those women who reported use 4–7 times per week experienced a significant 74% elevation in EOC risk (p for trend = 0.015). However, this was not a monotonic trend in that risk decreased between the second and third categories of use (from 1.34 to 1.16). Duration of use of talcum powder was associated with increased risk, although the pattern was also not clear-cut in that the point estimate peaked among those reporting 4–12 years of use and declined somewhat among those reporting longer duration of use (p for trend = 0.045). Cumulative use also demonstrated an uneven association with risk of EOC in that the point estimates peaked in the second and third quartiles of intensity but declined in the highest quartile of use.

The multivariate adjusted odds ratios were elevated primarily among those with a serous or mucinous invasive tumor and were lower among women with other cell types or with borderline tumors (Table III).

Risk of EOC associated with use of talcum powder was higher and statistically significant in those who reported first using pow-

TABLE III – FREQUENCIES, MULTIVARIATE-ADJUSTED ODDS RATIOS AND 95% CONFIDENCE INTERVALS FOR PERINEAL TALC USE AND EOC RISK BY INVASIVENESS AND HISTOLOGIC SUBTYPE, CENTRAL VALLEY OF CALIFORNIA, 2000–2001

Histologic subtype	Cases (%) (n = 256)[1]	Controls (%) (n = 1,122)[1]	Multivariate-adjusted OR (95% CI)
All invasive (n = 182)[1]			
− perineal talc use	98 (55.7)	696 (62.9)	1.0 (referent)
+ perineal talc use	78 (44.3)	410 (37.1)	1.51 (1.07–2.12)
Serous invasive (n = 92)[1]			
− perineal talc use	46 (52.3)	696 (62.9)	1.0 (referent)
+ perineal talc use	42 (47.7)	410 (37.1)	1.77 (1.12–2.81)
Mucinous invasive (n = 16)			
− perineal talc use	6 (37.5)	696 (62.9)	1.0 (referent)
+ perineal talc use	10 (62.5)	410 (37.1)	2.56 (0.89–7.39)
Endometrioid (n = 35)			
− perineal talc use	21 (60.0)	696 (62.9)	1.0 (referent)
+ perineal talc use	14 (40.0)	410 (37.1)	1.28 (0.62–2.62)
Clear cell (n = 12)[1]			
− perineal talc use	8 (72.7)	696 (62.9)	1.0 (referent)
+ perineal talc use	3 (27.3)	410 (37.1)	0.63 (0.15–2.64)
Other epithelial (n = 27)[1]			
− perineal talc use	17 (65.4)	696 (62.9)	1.0 (referent)
+ perineal talc use	9 (34.6)	410 (37.1)	1.06 (0.45–2.48)
All borderline (n = 74)[1]			
− perineal talc use	45 (61.6)	696 (62.9)	1.0 (referent)
+ perineal talc use	28 (38.4)	410 (37.1)	1.09 (0.65–1.83)
Serous borderline (n = 55)[1]			
− perineal talc use	32 (59.3)	696 (62.9)	1.0 (referent)
+ perineal talc use	22 (40.7)	410 (37.1)	1.28 (0.71–2.31)
Mucinous borderline (n = 19)			
− perineal talc use	13 (68.4)	696 (62.9)	1.0 (referent)
+ perineal talc use	6 (31.6)	410 (37.1)	0.76 (0.28–2.07)

Adjusted for age, race/ethnicity, duration of oral contraceptive use and breast feeding. [1]Numbers may not add up to total cases and controls due to missing data.

TABLE IV – FREQUENCIES, MULTIVARIATE-ADJUSTED ODDS RATIOS AND 95% CONFIDENCE INTERVALS FOR PERINEAL TALC USE AND EOC RISK BY TIMING OF USE, CENTRAL VALLEY OF CALIFORNIA, 2000–2001

Timing of talc use	Cases (%) (n = 256)[1]	Controls (%) (n = 1,122)[1]	Multivariate-adjusted OR (95% CI)
Year of first use			
Never use	143 (59.1)	695 (65.6)	1.0 (referent)
Before/during 1975	52 (21.5)	206 (19.4)	1.22 (0.84–1.77)
After 1975	47 (19.4)	149 (15.0)	1.92 (1.27–2.91)
Age at first use			
Never use	143 (59.1)	695 (65.7)	1.0 (referent)
< 20 years	30 (12.4)	169 (16.0)	0.95 (0.61–1.48)
20–24 years	26 (10.7)	61 (5.8)	2.41 (1.43–4.09)
≥ 25 years	43 (17.8)	133 (12.6)	1.80 (1.19–2.73)
First use before or after first birth[2]			
Never use	113 (59.2)	631 (65.6)	1.0 (referent)
Use at or prior to first birth	36 (18.8)	229 (23.8)	0.98 (0.64–1.48)
Use after first birth	42 (22.0)	102 (10.6)	2.51 (1.63–3.87)
Years since last use			
Never use	143 (59.1)	695 (65.6)	1.0 (referent)
Current users	32 (13.2)	133 (12.5)	1.27 (0.81–1.98)
1–2 years	27 (11.2)	61 (5.8)	2.40 (1.43–4.05)
3–20 years	20 (8.3)	83 (7.8)	1.57 (0.90–2.73)
> 20 years	20 (8.3)	88 (8.3)	1.13 (0.66–1.94)

Adjusted for age, race/ethnicity, duration of oral contraceptive use and breast feeding. [1]Numbers may not add up to total cases and controls due to missing data.–[2]Parous women only.

der after 1975 compared to those reporting use prior to that date (Table IV). Higher risk was found among those reporting first use at ages after age 20 compared to those who were younger at first use (Table IV). In addition, risk was elevated among those women who used talcum powder only after the birth of their first child, while no effect was seen among those whose first use occurred before their first child was born.

In an attempt to assess latency issues, we evaluated risk of EOC by categorizing participants by the numbers of years since last reported use of talcum powder (Table IV). The highest and significant risks were found among women who had stopped using talcum powder relatively recently (1–2 years prior to interview), while those who reported last using powders in the more distant past did not experience altered risk.

An evaluation of effect modification of the talcum powder-EOC relationship by gynecologic surgery, reproductive history, exogenous hormone use and BMI is presented in Table V. Women without a tubal ligation experienced higher talcum powder-associated risks than women with a tubal ligation and this result was statistically significant (OR = 1.54; 95% CI = 1.10–2.16). The interaction coefficient for the relationship between talc use and tubal ligation was not statistically significant. There was no mod-

TABLE V – FREQUENCIES, MULTIVARIATE-ADJUSTED ODDS RATIOS AND 95% CONFIDENCE INTERVALS FOR TALC USE AND RISK OF EOC BY LEVELS OF MODIFIERS IN THE CENTRAL VALLEY OF CALIFORNIA, 2000–2001

	Cases (n = 256)[1]	Controls (n = 1,122)[1]	Multivariate-adjusted OR (95% CI)
Tubal ligation			
Never talc use	29 (56.9)	161 (54.9)	1.0 (referent)
Ever talc use	22 (43.1)	132 (45.1)	0.88 (0.46–1.68)
No tubal ligation			
Never talc use	113 (57.4)	531 (65.8)	1.0 (referent)
Ever talc use	84 (42.6)	276 (34.2)	1.54 (1.10–2.16)
Hysterectomy[2]			
Never talc use	27 (50.0)	117 (58.8)	1.0 (referent)
Ever talc use	27 (50.0)	82 (41.2)	1.79 (0.91–3.52)
No hysterectomy[3]			
Never talc use	116 (59.5)	576 (63.7)	1.0 (referent)
Ever talc use	79 (40.5)	328 (36.3)	1.33 (0.95–1.87)
Ever pregnant			
Never talc use	118 (55.9)	648 (63.0)	1.0 (referent)
Ever talc use	93 (44.1)	381 (37.0)	1.44 (1.05–1.97)
Never pregnant			
Never talc use	25 (65.8)	47 (62.7)	1.0 (referent)
Ever talc use	13 (34.2)	28 (37.3)	0.93 (0.37–2.34)
Ever parous[4]			
Never talc use	113 (57.4)	633 (62.7)	1.0 (referent)
Ever talc use	84 (42.6)	376 (37.3)	1.34 (0.97–1.85)
Nulliparous[4]			
Never talc use	5 (35.7)	15 (75.0)	1.0 (referent)
Ever talc use	9 (64.3)	5 (25.0)	4.91 (0.68–35.25)
Ever OC use			
Never talc use	72 (51.4)	422 (57.7)	1.0 (referent)
Ever talc use	68 (48.6)	309 (42.3)	1.26 (0.86–1.83)
Never OC use			
Never talc use	71 (65.1)	272 (72.9)	1.0 (referent)
Ever talc use	38 (34.9)	101 (27.1)	1.63 (1.0–2.64)
HRT[5]			
Never talc use	54 (52.4)	220 (59.9)	1.0 (referent)
Ever talc use	49 (47.6)	147 (40.1)	1.41 (0.89–2.24)
No HRT[6]			
Never talc use	89 (62.2)	472 (64.4)	1.0 (referent)
Ever talc use	54 (37.8)	261 (35.6)	1.30 (0.87–1.93)
BMI $<$ 25			
Never talc use	55 (63.2)	311 (66.5)	1.0 (referent)
Ever talc use	32 (36.8)	157 (33.5)	1.23 (0.74–2.04)
BMI $\geq$ 25			
Never talc use	85 (53.5)	358 (59.1)	1.0 (referent)
Ever talc use	74 (46.5)	248 (40.9)	1.36 (0.92–1.99)

Adjusted for age, race/ethnicity, duration of oral contraceptive use and breast feeding. [1]Numbers may not add up to total cases and controls due to missing data.–[2]Includes women with $\geq$ 2 years since hysterectomy.–[3]Includes women with $<$ 2 years since hysterectomy.–[4]Gravida women only.–[5]Includes women with one or more years of use.–[6]Includes women with never use or $<$ 1 year of use.

ification within categories of prior hysterectomy, however. Higher risks were observed among those who were ever pregnant compared to those who were never pregnant. Talcum powder-associated risk was not different within the parous and nulliparous. Talcum powder-associated risk was higher (and significant) in women who never used oral contraceptives; however, the interaction coefficient was not statistically significant. Neither BMI or hormone replacement therapy (HRT) use appeared to modify the relationship of talc use and EOC risk.

DISCUSSION

The prevalence of talc use among controls in our study (37.1%) is similar to the average percentage of use among the control populations in a review of 14 studies (36.8% calculated from data presented in original study).[21] In the current analysis as in others,[11,21–24] a larger percentage of cases *versus* controls reported perineal exposure to talc. We found a slight trend of decreasing use with increasing age in control women but our findings were not as strong as those noted by Rosenblatt *et al.*[25] Other studies[21,24] have found increased use in both cases and controls over 50 years of age compared to their counterparts less than or equal to 50 years of age. In the present study, cases less than 50 years of age were more likely to have used talc *versus* women 50 years or older (47.7% and 39.9%, respectively). Different findings in talc use patterns between the present study and previous studies may be explained by differences in study locations, study time periods and age categories. Frequency of use in the current study was similar for both the younger and older groups in controls (38.2% and 36.4%, respectively).

Talc use was higher in white non-Hispanics compared to Hispanics in this study. However, the pattern of increased use in EOC cases for both groups contributed to the overall increased risk of EOC among talc users. Differential talc use by various ethnic groups and its relation to EOC risk has not, to our knowledge, been evaluated previously.

As in other studies,[21,25] we found that talc use increased with education level, although one earlier study reported the opposite finding.[24] Other studies have compared talc use in ever married to never married women and found either similar use in both groups for cases and controls[21] or increased frequency of use in ever married women.[24] In the current analysis, talc exposure was 43.8% for ever married cases *versus* 34.4% for never married cases. However, fre-

quency of use was similar between ever married and never married controls (37.2% and 36.0%, respectively). There was much greater use of talc among those born in the United States *versus* those born outside it.

The odds ratio comparing ever use to never use in this study (OR = 1.37; CI = 1.02–1.85) is similar to the results of a recent metaanalysis that pooled 16 studies (summary RR = 1.33; CI = 1.16–1.45).[4] When stratified by hospital- *versus* population-based studies, the population studies had a summary relative risk of 1.38 (1.25–1.52).

Cornstarch use and ovarian cancer has been evaluated in a small number of case-control studies[11,21,22,26] and have been reviewed with the conclusion that no relationship exists between cornstarch and EOC, although the number of study participants using cornstarch *versus* talc was small.[13] Our study was not able to differentiate between use of perineal powders containing talc and those containing cornstarch, which may have driven the odds ratio toward the null. Type of application, including direct application on the perineum, or indirect exposure from dusting sanitary napkins, underwear and diaphragms (storage) was also not assessed.

As in other studies,[4] the present study did not find a clear dose response based on duration of use or cumulative use. Limiting the analysis of dose response to women who reported ever use of talc did not affect the results (data not shown). The lack of dose response between talc use and EOC may be explained by the inability to quantify the actual amount of talc used per application and timing of the application.[21] Cramer *et al.*[21] propose that application during ovulation may pose more risk due to the possibility of talc entrapment in inclusion cysts. Harlow *et al.*[24] found little change in odds ratios after excluding use after tubal ligation or hysterectomy in their estimate of total lifetime perineal talc applications. However, when they excluded nonovulatory periods of exposure in their calculation, there was significant increase in risk. We were unable to exclude nonovulatory periods and talcum powder use after gynecologic surgery in our cumulative use calculations.

Our analysis found that talc use and EOC risk varied by histologic subtype, as have others who found that exposure to talc is a significant risk for invasive tumors[22] and specifically for serous invasive tumors.[21] Cook *et al.*[11] also found an increased risk of serous tumors (including both invasive and borderline) in talc users *versus* nonusers. Gertig *et al.*[27] have suggested that there are pathologic similarities between serous adenocarcinomas and mesothelioma that may explain findings of increase risk for serous invasive tumors in talc users. Harlow *et al.*[24] reported a significant increase in risk of either endometrioid or borderline tumors with talc use and suggest that variation in risk among histologic subtypes may be due to chance or a foreign-body effect unique to specific subtypes.

In a study of the mineral and chemical characterization of consumer talcum powder formulated prior to June 1973, almost half of the samples tested contained 1 of the 3 asbestos group minerals.[1] In 1976, talcum powder manufacturers instituted voluntary guidelines to prevent asbestos contamination in talc products,[24] but we did not find an increase in EOC risk with talc use on or before 1975; rather, we found that risk of EOC increased with use after 1975, which may be related to the recency of use. Harlow *et al.*[24] observed ovarian cancer risk was increased in women using talc products before 1960, although Chang and Risch[22] found no relationship between risk and use either before or after 1970.

In the current analysis, a statistically significant increase in EOC risk occurred with first use after age 20 compared to first use at younger ages. Controlling for recency of use did not change this finding. Other studies have reported either no trend with age at first use[21] or increased risk of EOC with first use at younger than age 20 and older than age 25.[24] Disagreement in findings between studies may be due to differences in age distributions and talc use patterns among study participants. Although we cannot directly assess risk during ovulatory *versus* nonovulatory periods, our findings of increased risk in adult women support the hypotheses of increased EOC risk with talc exposure during ovulatory periods and in parous reproductive tracts.

Cramer *et al.*[21] found that EOC risk was increased in parous women with talc use occurring before first birth, suggesting that prepregnancy ovarian tissue may be more vulnerable to talc damage because it has not undergone stromal differentiation (decidual reaction that occurs during pregnancy). However, their reference group was all parous women. In this analysis, we stratified parous women by never use, use before first birth and use after first birth. We found increased risk after first pregnancy. Anatomical changes in the genital tract after pregnancy may increase the possibility of talc migration to the ovaries.[28] Harlow *et al.*[24] suggest that pregnancy may increase risk due to its effect of increasing the size of the cervical opening into the uterus. In the current study, perineal talc use had no apparent impact on EOC risk among those women who had never been pregnant and parity was difficult to evaluate because of the small number of nulliparous women. In 2 prospective studies of talc use and EOC risk, there was no significant difference in parity between users and nonusers of talc.[25,27]

Harlow *et al.*[24] reported a significant increase in EOC risk if perineal talc use occurred in the last 6 months. We also found that recent users were at increased risk (even when we controlled for duration of use). It is noteworthy that a significant latency effect is well documented for asbestos exposure and development of both pleural and peritoneal mesotheliomas[29] while there appears to be no latency with talcum powder. The asbestos association has been reported from an occupational cohort mortality study where exposure is indirect and not the result of direct application, as is the case for talcum powder.[30] This may explain the differences between observed patterns of latency for asbestos and talcum powder. Additionally, risk of EOC with talc use may not be due to talc's chemical similarity to asbestos but rather due to the ovary's unique function, resulting in vulnerability to carcinogenesis from particulates such as talc.[8] In a study of gynecologic surgery and EOC, Green *et al.*[31] found that women reporting fallopian tubal occlusion, through tubal ligation or hysterectomy, were at decreased risk for developing EOC. They concluded that surgical tubal occlusion decreased EOC risk by preventing contaminants from reaching the ovary. Ness and Cottreau[32] proposed that the inflammatory response of the ovarian epithelium to various irritants may result in ovarian mutagenesis, tumor growth and tumor invasiveness. Cramer *et al.*[21] reported no association between EOC risk and talc use in women with a tubal ligation; however, risk remained nonsignificantly elevated in women with a hysterectomy. A recent prospective study[27] found that EOC risk in talc users was not modified by either tubal ligation or hysterectomy. The analysis was not able to determine the timing of talc use (before or after surgery). In a hospital-based case-control study, Wong *et al.*[33] found that risk of EOC with talc use was increased in women without gynecologic surgery and decreased in women with a history of tubal ligation or hysterectomy but neither finding was significant. They also were unable to delineate use before or after gynecologic surgery. Tubal ligation may limit a woman's exposure to contaminants more than hysterectomy since it is usually performed earlier in a woman's reproductive history, while she is still ovulating.[34]

Oral contraceptives (OCs) act by suppression of ovulation and the fact that elevated risks were found in those talcum powder users that never used OCs in this study suggests that uninterrupted ovulation with associated formation of inclusion cysts may enhance the impact that talcum powder may have on ovarian carcinogenesis. Unlike our study, however, Cramer *et al.*[21] and Harlow *et al.*[24] reported that OCs had no effect on talc use and EOC risk. A prospective study of talc use and ovarian cancer also found that the prevalence of OC use was similar in both users and nonusers of talc. However, these studies also reported lower percentages of OC use among both cases and controls (talc users and nonusers) than was found in the present study.

Our analysis found that BMI did not modify the risk associated with talc use and EOC in agreement with Cramer *et al.*[21] Talc use

was greater in women with a high *versus* low BMI for both cases and controls but the difference was not significant. Rosenblatt *et al.*[25] in a prospective study found that women in the highest BMI quartile were more likely to use perineal talc. They concluded that since some studies have found an increased risk for ovarian cancer in obese women, BMI may be a confounder of talc use and ovarian cancer risk. Harlow *et al.*,[24] however, reported no differential use of talc between leaner and heavier controls.

There are several limitations to this study that may limit interpretation of the findings. The sample size was relatively small and the response fraction lower than ideal. However, we have observed the same or similar relationships in our study between several risk factors such as OC use and parity, as has been observed in several earlier studies. Recall bias has also been implicated as a limitation in studies of talc and ovarian cancer.[35] However, findings in a prospective study, the Nurses' Health Study, in which exposure data were collected prior to diagnosis and hence free of recall bias, were similar to the present study finding for talc use and serous invasive ovarian cancer.[27] It has also been suggested that use of talc is habitual *versus* memorable and not likely to be subject to recall bias.[35] Huncharek *et al.*[4] suggested that the positive relationship between talc use and EOC risk found in a review of epidemiologic studies may also be explained by a treatment effect in prevalent cases. The present study used incident cases exclusively. The present analysis was also limited due to our inability to exclude use during nonovulatory periods and posttubal ligation or hysterectomy, nor were we able to differentiate between various formulations.

Research has provided little biologic or experimental evidence to support a relationship between talcum powder use and ovarian cancer risk. However, given the suggestive though uncertain role of talcum powder and EOC found in epidemiologic studies, including the present study, users should exercise prudence in reducing or eliminating use. In this instance, the precautionary principle should be invoked, especially given that this is a serious form of cancer, usually associated with a poor prognosis, with no current effective screening tool, steady incidence rates during the last quarter century and no prospect for successful therapy. Unlike other forms of environmental exposures, talcum powder use is easily avoidable.

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